REMARKS

I. Status Summary

Claims 1-18 and 20-22 are pending in the present application. Claims 1-11, 13-18 and 20-22 have been rejected by the U.S. Patent and Trademark Office (hereinafter the "Patent Office"). The Patent Office has withdrawn claim 12.

Claims 1, 7, 14, and 15 have been amended. Support for the amendments can be found throughout the specification as filed. No new matter has been added. Therefore, upon entry of Amendment A, claims 1-11, 13-18, and 20-22 will be pending in the subject application.

Reconsideration of the application as amended and further in view of the remarks set forth herein below is respectfully requested.

II. Election/Restrictions

The Patent Office has indicated that the elected species related to a conjugate of camptothecin glycine ester has been found to be free of the art. The Patent Office has further indicated that the search was extended to encompass the generic formulas of claim 1 and claims 7, which were also found to be free of art. Thus, the Patent Office has indicated that claims 1-11, 13-18, and 20-22 have been examined to the extent that the claims read on the elected species camptothecin glycine ester, which is an alkaloid. Applicants understand that the Patent Office has withdrawn claim 12 as being directed to non-elected subject matter.

Applicants gratefully acknowledge the Patent Office's indication that claims 1 and 7 relating to the elected species, camptothecin gylcine ester, are free of the art. In light of this indication on the part of the Patent Office, as well as in view of the remarks below, applicants respectfully ask that the Patent Office consider rejoinder of additional species of drug molecule.

III. Response to Rejections under 35 U.S.C. § 112, First Paragraph, Written Description Requirement

III.A. New Matter Rejection:

Claims 1-11, 13, 14, and 16-18 have been rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. The Patent Office contends that in the Preliminary Amendment filed on May 31, 2007, claim 1 was amended to recite a formula that has a carbon atom having a valency of 5. The Patent Office contends that the specification lacks support for such a formula.

Applicants respectfully traverse the rejection and offer the following remarks.

Applicants respectfully submit that the chemical structure presented in claim 1 of the Preliminary Amendment was the result of an inadvertent error related to reproducing the originally filed claims. Applicants respectfully submit that it was not intended that the chemical structure be different than that recited in claim 1 as originally filed. Applicants thank the Patent Office for bringing this matter to their attention and respectfully submit that claim 1 has been amended herein to replace the structure that includes a pentavalent carbon with the structure recited in original claim 1.

In addition to having support in original claim 1, support for the amendment can also be found in the instant specification as filed on page 2, line 20. No new matter has been added.

Applicants respectfully request that the rejection of claim 1 and its dependent claims 2-11, 13, 14, and 16-18 under 35 U.S.C. § 112, first paragraph, relating to new matter, be withdrawn. Applicants also ask that claims 1-11, 13, 14, and 16-18 be allowed at this time.

III.B. Other Written Description Requirement-Related Rejections:

Claims 1-11, 13-18, and 20-22 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. In particular, the Patent Office notes that for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. The Patent

Office contends that claims 1 and 7 recite that "P" is a "water-soluble polymer" but that the specification has specific examples only relating to polyethylene glycol and an oligopeptide of glutamic acid. The Patent Office contends that claims 1 and 7 recite that "X" is a linking group, but that "X" is not adequately defined in the claim or the specification. The Patent Office alleges that while claims 1 and 7 recite that "TA" is a "drug molecule" and claim 15 recites that "PT" is a "drug molecule," the term "drug molecule" lacks proper definition in that the number of specific drug compounds disclosed is not commensurate with the scope of the claims as recited. Finally, the Patent Office alleges that claims 17 and 21 recite "another therapeutically active ingredient," but that the specification does not provide a proper definition for the term.

After careful consideration of the rejection and the Patent Office's comments, applicants respectfully traverse the rejection and offer the following remarks.

Initially, applicants respectfully submit that there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. See Manual of Patent Examining Procedure (hereinafter "MPEP") § 2163.03, citing *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). Further, a description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See MPEP § 2163.04, citing *In re Marzoochi*, 439, F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

Applicants respectfully submit that the written description requirement related to claims drawn to a genus can be satisfied through sufficient description of a representative number of species by: (a) actual reduction to practice; (b) reduction to drawings; or (c) by disclosure of relevant identifying characteristics such as structure or other physical and/or chemical characteristics; by functional characteristics; or by a combination of such identifying characteristics. See MPEP § 2163 and *Eli Lilly* 119, F.3d at 1568, 43 USPQ2d at 1406. As further noted in MPEP § 2163, satisfactory disclosure of a representative number of species depends on whether one of skill in the art would recognize the applicant being in possession of the necessary common attributes possessed by the members of the genus in view of the species disclosed.

"There may be situations where one species adequately supports a genus." MPEP § 2163.

In general, applicants respectfully submit that the presently disclosed subject matter relates to a conjugate of a hydrophilic polymer-multicarboxyl oligopeptide moiety and a drug. See Instant Specification, page 2, lines 17-18. The conjugate can be used to improve the absorption of the drug, prolong therapeutic duration of the drug, increase the therapeutic effect of the drug, to reduce dosage, and to avoid toxicity and other side effects. See Instant Specification, page 3, lines 6-8. The instant specification further notes that advantages of the presently disclosed subject matter relate to the combination of the properties of the hydrophilic polymer portion of the hydrophilic polymer-multicarboxyl oligopeptide moiety (e.g., solubility, non-immunogenicity, and non-toxicity) and of the many drug loading sites of the multicarboxyl oligopeptide portion of the hydrophilic polymer-multicarboxyl oligopeptide moiety. See Instant Specification, page 4, lines 13-17.

Concerning the term "water-soluble polymer," which relates to the hydrophilic polymer portion of the hydrophilic polymer-multicarboxyl oligopeptide moiety, applicants respectfully submit that the instant specification specifically recites that the hydrophilic polymers used in the presently disclosed conjugates can include the following: polyethylene glycol (i.e., PEG), polypropylene, polyvinyl alcohol, polyacrylmorpholine or copolymers thereof. See Instant Specification, page 3, lines 20-22. The instant specification also describes a variety of different PEG derivatives by reference to a general structure (see Instant Specification, page 4, lines 22-32), and confirms that other analogs and derivatives of polyethylene glycol, including polypropylene glycol, polyvinyl alcohol, and polyacrylmorpholine and the like are envisioned as being useful in the conjugates of the presently disclosed subject matter. See Instant Specification, page 4, lines 33-35. Applicants further note that the instant specification describes that the hydrophilic polymer moiety is conjugated to the oligopeptide moiety by modifying a free end hydroxyl of the hydrophilic polymer. See Instant Specification, page 3, lines 23-25. Finally, as noted directly hereinabove, the instant specification recites that the hydrophilic polymer has properties that include, in addition to the water

solubility implied by the term "water soluble polymer," non-immunogenicity, and non-toxicity. See Instant Specification, page 4, lines 14-15.

Accordingly, applicants respectfully submit that the written description requirement with regard to the term "water-soluble polymer" as recited in claims 1 and 7 has been met, both by reciting a number of specific examples and generic structures for the hydrophilic polymer, as well as by providing functional description for the hydrophilic polymer.

Applicants respectfully disagree with the Patent Office's comment that the specification is silent with respect to any and all linking groups recited in the claims. In particular, applicants respectfully submit that the instant specification describes, as linking groups, the following specific structures: $(CH_2)_i$, $(CH_2)OCO$, $(CH_2)_iNHCO$ and $(CH_2)_iCO$, O and NH. See Instant Specification, page 7, lines 18-20. Further, applicants note that the instant specification recites that the hydrophilic polymer-glutamic acid oligopeptide moiety of the conjugate can be synthesized by various known methods in the art. See Instant Specification, page 6, lines 13-15. In particular, the instant specification describes that the terminal group of the hydrophilic polymer (i.e., the terminal group of "P" of the formula of claim 1) can be activated to react with the amino or carboxyl group of the oligopeptide via amination, carboxylation, or by modification with acyl chloride, hydrazine, maleimide, pyridine disulfide, etc. See Instant Specification, page 6, lines 16-28. In view of these types of activation chemistries described in the specification, and in view of the placement of X in the formula recited in claim 1 (i.e., between P and the NH atoms of the oligopeptide moiety), applicants respectfully submit that one of ordinary skill in the art would understand the types of linking groups encompassed by X. Accordingly, applicants respectfully submit that the written description requirement with regard to the term "linking group" for X in claims 1 and 7 has been met.

Regarding the term "drug molecule," applicants respectfully submit that, as noted by the Patent Office, the instant specification describes drug molecules as including a variety of different known classes of compounds, such as amino acids, proteins, enzymes, nucleosides, saccharides, organic acids, glycosides, flavonoids,

quinones, terpenoids, phenylpropanoid phenols, steroids and glycosides thereof, alkaloids and the like. See Instant Specification, page 8, lines 5-8. Applicants respectfully submit that this listing specifically recites at least thirteen "species" of drug molecules. The instant specification also recites that the drug molecule can be an active ingredient from a plant, specifically reciting the individual molecules cinobufagin (a steroid), clycyrrhetinic acid (an organic acid) and scopoletin (a phenylpropanoid phenol) as being examples of such drugs. See Instant Specfication, page 8, lines 9-11. The specification further notes that the drug molecule can be a drug used in the treatment of tumors, specifically reciting paclitaxel (a terpenoid), camptothecin (an alkaloid), hydroxylcamptothecin (an alkaloid), etoposide (a non-alkaloid), and derivatives thereof. See Instant Specification, page 8, lines 11-13. In addition, working Examples 3 and 4 relate to conjugates of the terpenoid paclitaxel. See Instant Specification, page 10, line 30 to page 11, line 15. Working Example 5 relates to a conjugate of the alkaloid camptothecin glycine ester. See Instant Specification, page 11, line 20 to page 12, line 6. Working Example 6 relates to a conjugate of the steroid cinobufagin. See Instant Specification, page 12, lines 11-20. Working Example 7 relates to a conjugate of the organic acid clycyrrhetinic acid. See Instant Specification, page 12, lines 25-36. Working Example 8 relates to a conjugate of the phenylpropanoid phenol scopoletin. See Instant Specification, page 13, lines 5-15.

Additionally, applicants respectfully submit that the instant specification recites that the drugs of the presently disclosed subject matter can comprise functional groups such as amino, carboxyl, and hydroxyl groups and, *in vivo*, can conjugate to biomolecules including monosaccharide, polysaccharide, nucleoside, polynucleoside and phosphoryl groups. See Instant Specification, page 6, line 30 to page 7, line 3. The instant specification notes that the hydrophilic polymer-multioligopeptide moiety can conjugate to the drug molecules in the same way as the biomolecules do, thereby increasing the drugs physiological half-life and therapeutic duration. See Instant Specification, page 7, lines 4-6.

Thus, applicants respectfully submit that the term "drug molecule" has been described by a sufficient number of species (including various specific individual drugs

and specific compound classes) as well as by functional language in order to meet the written description requirement of 35 U.S.C. § 112, first paragraph.

Concerning the recitation of "another pharmaceutically active ingredient" in claims 17 and 21, applicants respectfully submit that one of skill in the art after review of the claims and specification would understand that such recitation refers to the inclusion in the claimed composition of a second medically active agent in addition to drug molecule TA or PT. Applicants respectfully submit that the language "another and "pharmaceutically active" should be sufficient in fulfilling the written description requirement. Further, applicants respectfully submit that it would be understood after review of the instant specification, that the pharmaceutically active agents can include other drug molecules. As noted hereinabove, the term drug molecule can include a variety of classes of molecule (e.g., amino acids, proteins, enzymes, nucleosides, saccharides, organic acids, glycosides, flavonoids, quinones, terpenoids, phenylpropanoid phenols, steroids and glycosides thereof, alkaloids and the like).

Accordingly, applicants respectfully request that the rejection of claims 1-11, 13-18, and 20-22 under 35 U.S.C. § 112, first paragraph, relating to the written description requirement be withdrawn, and further ask that claims 1-11, 13-18, and 20-22 be allowed at this time.

IV. Response to Rejections under 35 U.S.C. § 112, First Paragraph, Enablement Requirement

Claims 1-11, 13, and 14 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. In particular, the Patent Office alleges that the structure of the compound in the formula shown in claim 1 depicts a carbon atom having a valency of 5. The Patent Office alleges that the specification does not enable one of ordinary skill in the art how to make or use a conjugate having a formula of claim 1.

After careful consideration of the rejection and the Patent Office's comments, applicants respectfully traverse the rejection and offer the following remarks.

Applicants respectfully submit that as described hereinabove, claim 1 has been amended to replace the structure having a pentavalent carbon with the structure recited in original claim 1 and on page 2, line 20 of the instant specification as filed. Applicants respectfully submit that the atoms of the formula recited in claim 1 have proper valencies. Applicants further respectfully submit that the specification as filed would enable one of ordinary skill in the art in making the claimed conjugates. For example, applicants respectfully submit that Figures 2 and 3 and Examples 3-8 of the instant specification relate to the preparation of specific drug conjugates embodied by the formula recited in claim 1.

Accordingly, applicants respectfully request that the rejection of claim 1 and its dependent claims, claims 2-11, 13, and 14, under the enablement requirement of 35 U.S.C. § 112, first paragraph, be withdrawn. Applicants also respectfully ask that claims 1-11, 13, and 14 be allowed at this time.

V. Response to Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1-11, 13-18, and 20-22 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. More particularly, the Patent Office contends that claim 1 recites a carbon atom having a valency of 5, which is alleged to be indefinite because carbon has a valency of 4. The Patent Office contends that claim 7 recites a limitation "P is a water soluble polymer" when the variable "p" is not found in the formula presented in claim 7. Finally, the Patent Office notes that claims 14 and 15 recite "derivatives thereof" in defining antitumor agents and drug molecules. The Patent Office contends that neither the claims nor the specification define the nature of such derivatives.

After careful consideration of the rejection and the Patent Office's comments, applicants respectfully traverse the rejection and offer the following comments.

Applicants respectfully submit that, as described hereinabove, claim 1 has been amended to replace the formula having a pentavalent carbon with the formula of claim 1 as originally filed and as also recited on page 2, line 20 of the instant specification. In addition, applicants respectfully submit that claim 7 has been amended herein to delete

the phrase "P is a water soluble polymer." Further, claims 14 and 15 have been amended to replace the word "derivatives" with the word "esters." Support for the amendment to claims 14 and 15 can be found in the instant specification as filed, which recites an embodiment relating to camptothecin glycine ester, an ester derivative of the drug camptothecin. See Figure 3 and Example 5, page 11, line 20 to page 12, line 6.

Applicants respectfully request that the rejection of claims 1-11, 13-18, and 20-22 under 35 U.S.C. § 112, second paragraph, be withdrawn and ask that claims 1-11, 13-18 and 20-22 be allowed at this time.

CONCLUSIONS

Should there be any minor issues outstanding in this matter, the Examiner is respectfully requested to telephone the undersigned attorney. Early passage of the subject application to issue is earnestly solicited.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any fees associated with the filing of this correspondence to Deposit Account Number **50-0426**.

Respectfully submitted,

JENKINS, WILSON, TAYLOR & HUNT, P.A.

Date: December 6, 2007 By: _____

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